REMARKS

Claims

Each of the claims herein is characterized by a requirement that a cell which overexpresses ErbB2 is contacted with an affective amount of an isolated antibody that binds to the epitope on ErbB2 bound by antibody 7C2, except Claim 63. Claim 63 is considered, separately, below. The remaining claims addressed herein, Claims 28-40, 42-62 and 64, all other claims pending, are addressed together, below, because the rejections thereof all fail from a common problem.

The Rejections

The Examiner rejects various claims as met, or obvious, by Shepard (1991) or Lewis (1993), or as obvious over Shephard or Lewis taken in view of a variety of secondary references, including Fendley, et al. (1990). Each of these references are linked because they refer to monoclonal antibodies 7C2 and 7F3, thus, for instance, Shephard identifies a panel of nine (9) "$p185^{HER2}$ monoclonal antibodies", page 119, right-hand column, which include both 7C2 and 7F3. These are referenced, for example, in Figure 2, and Tables I and II. Lewis contains the same type of incidental disclosure of 7C2 and 7F3, see Table II, and the brief discussion of these antibodies at the bottom of the left-hand column of page 259. The secondary reference relied on in all obviousness rejections, Fendley, also work of the inventor herein, contains fundamentally the same tabular information contained in Shephard, see Figure I, and characterization in Table I, page 1555, but no additional information regarding these particular antibodies.

As recognized by the Examiner, these antibodies, and other antibodies that bind the same domain, have been shown in the specification to exhibit unusual properties, including, but not limited, to induction of cell death, that is, apoptosis. As clearly acknowledged by the Examiner, pages 5-7, apoptosis is a different kind of cell death than that affected through many other

antibody-mediated treatments, including "complement, phagocytic cells, cytotoxic drugs or growth inhibitory agents", outstanding Office Action, page 6, bottom.

It is of particular note that none of the references identify a publically available source of antibodies that bind to the 7C2 epitope. None of them provide specific indications of how to obtain an antibody that binds to a 7C2 epitope. None of the references provide instructions or an indication to search for, an assay to isolate, or otherwise identify antibodies which induce cell death through apoptosis. Fundamentally, the references do nothing to put one of ordinary skill in the art in possession of antibodies other than those available prior to the effective filing date of the application, such as antibody 4D5. While this antibody is a valuable anti-erbB2 antibody, it does not bind to the 7C2 epitope, nor do the references indicate it exhibits strong apototic properties, that is, induces cell death, alone. As discussed in more detail below, Applicants respectfully submit that such references fail to satisfy the *prima facie* burden imposed on the Examiner.

The Legal Standard

Certainly for at least the last half of the twentieth century, and up to today, it has been the standard of the law that to support a rejection for anticipation or obviousness under 35 U.S.C. §102/103, the burden is on the Office, and the Examiner, to come forward with a *prima facie* case of obviousness. Specifically, the Office must identify the art relied on, and the specific facts identified, to support the rejection. In re Thrift, 298 F.3d 1357, 1363, 63 USPQ.2d 2002 (Fed. Cir. 2002) and In re Piasecki, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). The burden shifts to the applicant only to rebut a *prima facie* case. Piasecki, supra.

It has been a standard of the law for the last 185 years that a *prima facie* case of anticipation or obviousness is not made out unless the disclosure is sufficient to permit the public (as represented by one of ordinary skill in the art to practice the invention) to practice the

invention. Seymour v. Osborne, 11 Wall. 516, 555 (1820). This principle has been reestablished many times, and is consistently applied where the technology involved is in the course of being developed, and the art cited is discussive, rather than exemplary. See, e.g., Ex parte Gould, 231 USPQ 943, 945 (BPAI 1986), citing In re Legrice, 301 F.2d 929, 133 USPQ 365, 370-376 (CCPA 1982). The discussion in Legrice is particularly apt, as it discusses, at length, the rationale behind requiring a reference cited pursuant to 35 U.S.C. §102(b), the statutory authority relied on by the Examiner herein, to be "self-enabling" given the policies behind the statute. It should be noted that it continues to be the standard of the law today - a challenge to a patent claim based on a reference that does not, in and of itself, when coupled with the understanding of those of skill in the art as of the filing date of the application in question, put the public in possession of the invention cannot support a *prima facie* case of obviousness or anticipation, no matter how closely related to the subject matter it is. See, e.g., Reading & Bates Construction Co. v. Baker Energy Resources Corp., 223 USPQ 1168, 1172 (Fed. Cir. 1984) and Preemption Devices, Inc. v. Minnesota Mining and Manufacturing Co., 732 F.2d 903, 906, 221 USPQ 841, 843 (Fed. Cir. 1984).

Applicants note with specificity that at no time during prosecution of the above-captioned application, which stretches back to 1997, has the Examiner ever identified the basis for the factual conclusion that the antibodies of Shephard, Lewis and Fendley, specifically, 7C2 and 7F3, were available to those of ordinary skill in the art. Indeed, the Examiner has inverted the burden, repeatedly. For example, in Paper No. 30, pages 2-3, the Examiner advanced, as a reason for maintaining the rejection that "there is no declaration from Genentech stating public availability or lack thereof" with regard to the antibodies of Shephard. Clearly, this is an inversion of the applicable legal burden. See, to the same affect, the outstanding Office Action, which characterizes the question only, page 3, "if the required antibody is in public use in the method, or

can be obtained by the public . . . then the prior art meets the requirements of 35 U.S.C. §102(b)". Office Action, page 3.

Fundamentally, this is a misapplication of the burden imposed by law. Simply pointing to the appearance of the name of the antibodies in the prior art does not establish their possession by the public. Indeed, Congress, and the Patent Office, have recognized the fact that biological materials may not be available simply because they are "identified", and accordingly, have placed the burden for public availability on an applicant. "To avoid the need for a deposit . . ., the biological material must be both known and readily available - neither concept alone is sufficient." MPEP, §2404.01. See also, Ex parte Humphreys, 24 USPQ.2d 1255 (BPAI 1992). In fact, Congress and the Patent Office have so clearly recognized the problems with public availability of biological materials that a separate set of regulations, 37 C.F.R. §1.801 et seq. has been created, and further, those Rules specify that not just any deposit will satisfy the standard set forth above, "known and readily available". The standards set forth in 37 C.F.R. §8.08(a) must be satisfied before biological materials, such as antibodies, are considered by the Office to be "known and readily available." Among these requirements is the requirement that "all restrictions imposed by the depositor . . . will be irrevocably removed." The MPEP specifically indicates that if these standards are not satisfied, the deposit cannot be relied upon to establish that the biological materials, in this case, antibodies, are "known and readily available." Unless this threshold is met, the legal standard is not satisfied. It has not been met in this case.

Application of the Law to the Facts

As noted above, the rejections fail to point to a source of public availability of the antibodies. Although the Examiner, occasionally, referred to the procedural details contained in the references, the references uniformly refer to Fendley, the secondary reference cited, for this procedure. See, e.g., Shephard, page 119, left-hand column, and bibliographic reference 28. The

"generation of monoclonal antibodies specific for $p185^{HER2}$ appears, in its entirety, in the single paragraph bearing that title at page 1551, left-hand column of Fendley. Nothing therein is sufficient to allow one of skill in the art to reliably obtain antibodies that bind to the 7C2 epitope, or that exhibit apoptotic behavior. The Examiner has not advanced any such evidence. Accordingly, Applicants respectfully submit that the references assembled fail to support the burden imposed, that is, fail to make out a *prima facie* case of obviousness, because they fail to put the public in possession of the invention in a way that allows those of skill in the art to practice the methods claimed herein. For this reason alone, the rejection is respectfully traversed.

The rejection is further traversed because the evidence of record demonstrates that the antibody was not available in a form mandated by the Patent Office, and by Congress, to satisfy the requirements of enablement. Specifically, the antibody was not available without restriction, in accordance with the requirements of 37 C.F.R. §1.808, nor was it otherwise available without restriction. The Declaration of Phillips, of record, clearly establishes that the antibodies "were not disclosed in the references in such a way that a skilled person could have reproduced those particular antibodies based on the references." Phillips is in a position to know and understand this, as she is one of the named co-inventors, and one of the co-authors of the references (Gail D. Phillips and Gail D. Lewis are one in the same). The Examiner does not appear to take issue with that conclusion drawn by Lewis.

Rather, at least in recent Office Actions, the Examiner has asserted, without pointing to any particular support, that one of ordinary skill in the art could get the antibodies required by the claims herein from Genentech. Again, the record establishes a different conclusion. The Declaration of Phillips/Lewis also establishes that any laboratory seeking access to the antibodies would have to be a bonafide research laboratory, and could not transfer this research material to others outside the laboratory receiving the research material. Indeed, the materials provided, and

the results of the research, could not even be provided to third parties prior to receiving Genentech's approval. Unquestionably, access to the antibodies provided pursuant to the MTA, did not meet what Congress and the PTO have specified is a requirement for "known and readily available" materials, it was not available without restriction.

In the face of this evidence, the Examiner does not point to any other source for the antibodies in question. The Examiner asserts, without citation or rationale, that if the antibody "can be obtained by the public (which it can be as long as the requestor is willing to meet the MTA requirements), than the prior art meets the requirements of 35 U.S.C. §102(b) and 35 U.S.C. §103(a)." Office Action, page 3. Respectfully, Applicants disagree, on two counts. First, the Examiner is wrong in stating "the materials are available to any investigator who agrees to the restriction of the Genentech MTA." Office Action, page 3. That's not true. As established by the MTA, and the Declaration of Phillips, first, the "investigator" must establish itself as a research laboratory. This is not what is contemplated in 37 C.F.R. §1.808. Second, even if the investigator is a research laboratory, and does agree to the restrictions, it can no longer use the antibody without restriction, or transfer to a third-party, again a requirement of 37 C.F.R. §1.808. Applicants appreciate the Examiner's discussion of "threshold" requirements in the outstanding Office Action, page 3, item 5, but respectfully submit that the law does not reflect such threshold issues. There are only two issues. First, is the biological material publically available, without restriction, such that it is "known and readily available." If that question is answered negatively, the burden imposed of making a *primae facie* case is not shouldered, and the rejection fails of its own weight. This is not a "threshold" it is a substantive requirement of the law.

Fundamentally, limited availability is the not the standard of the law. The rejection should be withdrawn.

Claim 63

Claim 63 is distinguished from the remaining claims in that it does not require use of an antibody that binds to the 7C2 epitope. Rather, it is directed to a method for inducing cell death which comprises exposing a cell overexpressing ErbB2 to an effective amount of an isolated antibody. The claim is particularly characterized by the requirement that the isolated antibody induce cell death. While the Examiner is correct that the claim embraces adding any other agent to the system, the claim specifies that it is the isolated antibody that induces cell death. The Examiner has rejected this claim over Shephard, based on the teaching of Shephard directed to mAb 4D5, further noting that 4D5 and 7C2 and 7F3 "inhibit SKBR3 proliferation." Respectfully, Shephard does not show that 4D5, as an isolated antibody kills any cell. 4D5 acts in a variety of ways, but Shephard does not show 4D5 to be effective in inducing apoptosis. The Examiner asserts, page 5 of the outstanding Office Action, that "the claim is not restricted only to apoptosis, nor is the language restricted as to the use of other reagents, such as complement, phagocytic cells, cytotoxic cells or drug inhibitory agents, in addition to the antibody." While these things can be added, the claim is not satisfied unless the antibody, alone, induces cell death. In the case of complement, antibody dependent cellular cytotoxcitity, phagocytic cells, cytotoxic drugs or growth inhibitory agents, any cell killing that occurs does not occur due to the isolated antibody, but the conjoint action of the antibody with something else, some other agent harnessed by the immune system or administered to the patient. Only through apoptosis does an antibody act to induce cell death, or otherwise achieve cell killing, without a secondary actor. Nothing in Shephard suggests that the antibodies in question, or indeed, any antibody, would be effective, alone, as a cell killing agent, that is, exhibit apoptotic activity. Accordingly, the rejection necessarily fails.

Applicants respectfully submit that they are entitled to a clear identification of that aspect

of the prior art the Examiner relies on to establish antibodies satisfying the method claim requirements presented were "known and readily available" to those of ordinary skill in the art more than a year prior to the filing date Applicants are entitled to pursuant to 35 U.S.C. §120. If, in fact, the sole basis for that assertion is the restricted availability of antibody 7F3 or 7C2 under the Genentech MTA available at the time, (the MTA of record is in fact the MTA employed between 1993 and 1996 as made clear by the Phillips Declaration) Applicants respectfully request the Examiner so indicate, and explain how such restricted availability satisfies the requirements of 37 C.F.R. §1.808, or other regulatory or statutory provision so satisfying the requirements of the law. Applicants respectfully submit that in the absence of such identification, an affidavit or declaration from the Examiner establishing that those of skill in the art would have been able to freely access the antibody in question is required, to support the outstanding rejection.

SUMMARY

All claims pending stand rejected over art that does not either teach those of ordinary skill in the art how to make the antibodies required by the methods advanced herein, nor do they identify a source of the antibodies that was "known and readily available" to those of ordinary skill in the art, prior to Applicants' effective filing date. As such, they fail to make out a *prima facie* case of anticipation or obviousness. The rejections are respectfully traversed. As the claims are otherwise in compliance with Title 35, they are in condition for allowance, and an early and favorable action thereon is respectfully requested.

Respectfully submitted,

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